Review Article

Frontal fibrosing alopecia: state of the art and future directions

Joana R. Lascasas[1]*, Joana S. Peixoto[2], Sofia C. Vedor[3]

[1]Family Medicine UCSP Caminha, Unidade Local de Saúde do Alto Minho, Viana do Castelo, Portugal
[2]Family Medicine USF Mais Saúde, Unidade Local de Saúde do Alto Minho, Viana do Castelo, Portugal
[3]Aesthetical Medicine, Centro Internacional de Estudios de Postgrado (CIEP), Distance University of Madrid, Cordoba, Spain

*Correspondence:
Dr. Joana R. Lascasas,
E-mail: joanaresselascasas@gmail.com

ABSTRACT

Frontal fibrosing alopecia (FFA) is a primary lymphocytic cicatricial alopecia, characterized by recession of frontotemporal hairline with frequent involvement of eyebrows and affecting occasionally other body areas. Entitled an emerging epidemic, due to its rising incidence, FFA etiology remains unclear without proven effective therapies. This study reviews relevant publications on FFA, regarding pathogenesis, clinical findings, histology along with treatment and prognosis. A bibliographic search was conducted in the main international databases, using the term 'FFA'. Guidelines, observational studies, randomized controlled trials, reviews, systematic reviews and meta-analysis regardless of publication date, presented in English, Portuguese or Spanish, were included in this review. 50 publications were fully analysed. The majority of FFA cases were observed in postmenopausal women, although both men and women from younger ages can be victims. From an etiological point of view, immune-mediated hypothesis is widely spread, as stem cells localized in the bulge region of the follicle are destroyed by an inflammatory infiltrate. However, environmental factors raised interest, since sunscreen use was related to a bigger incidence of FFA. Three clinical patterns have been described. Yet the failure to use standardized assessment methods in addition to the absence of prospective studies evaluating available therapies, do not concede comparable data. Spontaneous stabilization of disease can occur, but regrowth was only seen in scarce cases. Outcomes from randomized controlled trials and prospective studies are missing to draw further understanding of FFA.

Keywords: Alopecia, Lichen planopilaris, Follicular lichen planus, Scarring alopecia, Lymphocytic cicatricial alopecia

INTRODUCTION

FFA first described by Kossard in 1994 is a primary lymphocytic cicatricial alopecia mostly affecting the frontotemporal hairline and eyebrows.[1] Despite its distinctive clinical findings, FFA is often referred as a variant of lichen planopilaris (LPP) by its indistinguishable histology.[2] Postmenopausal women are more likely to be involved, despite young women and men may also be affected. Its worldwide incidence has increased, being labelled as an emerging epidemic.[2] Case reports describe not only Caucasian, but also Asian and African patients.[1,2]

The etiopathogenesis is still on debate. Immune-mediated mechanisms as well as genetic, hormonal and environmental factors play a role in current research towards understanding this disease.[1] Moreover, sunscreens and leave-on facial products raised interest, due to FFA rising cases over the last decade.[3] Compelling

treatments have been reported although neither guidelines nor firm evidence exists.

Thus, the aim of this study was to review the relevant publications regarding FFA. This study will focus on the pathogenesis, clinical features, histology as well as treatment and prognosis of FFA.

A comprehensive research supports an early recognition of the disease by physicians, promoting a less extent of hair loss and higher quality health services.

METHODS

The search term "FFA" was used on May 2020. PubMed, Cochrane library, NHS national electronic library, BMJ evidence-based medicine, DARE, bandolier, national guideline clearinghouse and Canadian medical association databases were accessed for guidelines, observational studies, randomized controlled trials, reviews, systematic reviews and meta-analysis in English, Portuguese or Spanish. Publication dates were not restricted.

In addition, certain case reports addressing important and newer topics of the disease were included. By assessing titles and abstracts, publications were excluded if not meeting inclusion criteria or diverging from the study purpose. Accordingly, 50 publications were included and fully analysed.

PATHOGENESIS

The definite pathogenesis of FFA is not yet recognised.

Immune-mediated

FFA expresses an example of immune privilege loss, leading to an upregulation of major histocompatibility complex (MHC) class I and II. Hair stem cells placed in the infundibulo-isthmic (bulge) region of the follicle are attacked by an immune-mediated inflammatory infiltrate, more recently characterized by a prevalence of CD8^{+} T lymphocytes.[4]

Peroxisome proliferator-activated receptors (PPAR) are nuclear hormone receptors that regulate gene transcription.[5] PPAR-γ is predominantly expressed in sebocytes, including the pilosebaceous units and the adipose tissue. Its activity is predominant during the anagen phase of hair cycle, being the key to control the action of TGFβ1 in supressing fibrogenesis.[5,6] Although deletions have been shown.[7] These transformations may account for the development of scarring alopecia and need further investigation on causative elements.

Hormonal

Sex hormones have long been theorized to play a role in the development of FFA, as a result of the postmenopausal preponderance.[8] However, some authors consider that there must be another explanation for FFA growing incidence.[3]

Despite disagreements, dehydroepiandrosterone (DHEA) and its sulphated products (DHEAS) have higher levels between 25 and 30 years, then starts decreasing and reaches only 10 to 20% of peak levels at 60 years.[6] DHEA is an immunomodulatory hormone essential for PPAR functions, highlighting the potential inhibitory effects on the TGFβ pathway.[9]

The relation between the activity of DHEA and FFA is also indicated by the reduction of DHEA levels in other conditions, for example idiopathic pulmonary fibrosis.[10] Skin cells retain the necessary network to synthesise dihydrotestosterone (DHT) and testosterone from DHEA.[11] However, depending on the serum concentrations of these hormones, DHEA has been shown to behave as a partial agonist of androgen receptors, and therefore probably has an anti-androgen effect. Contrarily, DHEA is a full agonist of oestrogen receptors with comparable or slightly greater response than oestradiol. Hence, DHEA is considered a potentially effective therapy for FFA.[9]

Hypothyroidism and FFA have been associated, due to the higher incidence of thyroid abnormalities in female patients with FFA diagnosis. This phenomenon conducted some authors to recommend a systematic evaluation of thyroid, through laboratory and imaging studies in the initial workup of patients with FFA.[12]

Genetic

The genetic hypothesis is supported by evidence of FFA in first-degree relatives.[13] Autosomal dominant inheritance with incomplete penetrance is suggested, nevertheless the potential role of epigenetics.[14]

Environment

Beyond the growing incidence, typical later-life clinical findings aroused interest in potential environmental triggering factors.[14]

Aldoori et al observed a statistical significance in FFA patients with sunscreen use compared with controls. On patch, reactions to linalool hydroperoxide and balsam of Peru were also commonly found in these patients.[3] Recent studies provided evidence that sebaceous glands perform a crucial function in skin detoxification, although its activity decreases with age.[15] It has been discussed if environmental mechanisms result of specific compounds on facial products or represent a manifestation of a prolonged retention within the hair follicle, due to impaired function of sebaceous glands.[3] Other chemical treatments, such as colouring and perming, do not have strong evidence supporting their potential harm effects in FFA.[3,16]

Currently, Robinson et al appeal for cautious conclusions, based on low incidence of FFA compared to the incidence of sunscreen use, and the absence of relationship between alopecia and sunscreen use on the rest of body surface.[8]

Connubial cases were described in genetically unrelated couples, still addressing the possibility of a common environmental factor in the aetiology of FFA.[17]

CLINICAL FEATURES AND HISTOPATHOLOGY

Three clinical patterns of hair loss have been outlined: linear, diffuse zig-zag and pseudo-fringe. Linear pattern is defined as a band of uniform frontal hairline recession in the absence of loss of hair density behind the hairline. Diffuse zig-zag pattern is the same as linear but with at least 50% decreased hair density. Pseudo-fringe sign is characterized by a retention of hairs along the frontotemporal hairline with a clinical aspect analogous to fringe sign, evidenced in traction alopecia.[18] Hair loss may progress sub clinically, meaning that a significant amount of hair is usually lost before the alopecia is apparent, making it difficult to precisely determine its onset.[16] Vellus hair depletion has been evoked as a relevant clinical and dermoscopic finding, uncovering the remaining lonely terminal hairs.[19] Periauricular and occipital regions are reported in scarce cases.[20] Periauricular wrinkles were significantly increased in FFA patients.[21] Loss of eyebrows occurred in 50-83% of cases, while eyelash volume loss has been less documented (0-77%).[14] Subjective symptoms (pruritus, burning sensation and tenderness) are equally evidenced in both genders, enhancing the loss in quality of life and the relevance of clinical interview on these patients.[22]

Effects in other body areas, for instance axillae, pubis and limbs can occur in up to 53% of patients.[23] Facial papules (temple, cheeks and chin), hypo-/hyperpigmented macules, protrusion or depression of facial veins and glabellar red dots were also seen.[22] Of note, systemic involvement can either precede or succeed the scalp lesions.[24] No correlation was found between severity of FFA and the duration of the disease.[25] Stabilization of FFA may happen spontaneously or as a result of the induced treatment.[18, 25]

Trichoscopy is useful not only for guiding clinical diagnosis, but also choosing the best target zone to biopsy. In FFA, the most commonly perceived signs have been empty follicles/yellow dots, privation of follicular ostia, presence of lonely hair and follicular scaling and/or erythema.[25] Recently, pili torti was noted in FFA patients.[26] These features are related to histological findings, illustrating a lymph histiocytic infiltrate and prominent follicular fibrosis located in infundibulo-isthmic (bulge) region of the follicle.[24] Nonetheless, Doche et al revealed that apparently unaffected scalp areas presented lymphocytic follicular inflammation around isthmus/infundibulum areas in 64.2% of biopsy specimens and follicular fibrosis in 17.8% of cases.[24]

Again, histological features seen in FFA are identical to LPP.[24] Furthermore, clinical affected areas and disease progression are generally distinctive, with LPP having a rapid and devastating evolution, due to different depth extension of inflammation.[27] Direct immunofluorescence showed a predominance of negative results in FFA, contrasting with LPP findings.[28]

DIAGNOSIS

Scalp biopsy is the gold-standard for diagnosis, although it can be made clinically through physical examination and trichoscopy.[29] Differential diagnosis of FFA is critical for a systematic evaluation, enhancing an accurate patient analysis (Table 1).[30]

Given the inapplicability of histopathology for follow-up, optical coherence tomography (OCT) is being researched for potential monitoring of FFA. Vasquez-Herrera et al. in a case control-study, including 4 FFA patients observed a partial/complete loss of follicular openings and an erratic increased epidermal thickness in the inflammatory hairline. On the other hand, alopecia bands were characterized by a reduced epidermal thickness, representing the established fibrosis tissue, rather than an increase of collagen deposition. These patients also revealed a loss of superficial vascular density, compensated by the increase in deeper levels.[29]

At the beginning, the severity of FFA has been classified using the LPP Activity Index (LPPAI).[31] However, soon was criticized based on its subjective features and the similarities with LPP exclusively in histology.[32] Then, the fibrosing alopecia severity index (FFASI) was proposed by Holmes at al including two major sections, A and B. FFASI-A employs clinical images of the hairline, divided into four sections. Alopecia severity is then ranked 1-5 based on hairline recession. Other hair loss and additional findings are further scored as no loss, partial loss, and total loss and present or absent, respectively. All scores may be combined to give a maximum score of 100. FFASI-B evaluates the same features, but it includes scores to assess inflammation and density as well involvement of other body regions.[33] Despite all efforts, this scale set up controversies, considering the absence of internal validity and practicality.[34] Afterwards, Saceda-Corralo et al projected the FFA severity score (FFASS), which intended to be simpler and user-friendly. Thus, this score assessed for internal and external validity, comprehended less clinical parameters and lacked trichoscopic evaluation, important to improve the appraisal of inflammation.[32] In recent past, the trichoscopic visual scale demonstrated a strong correlation between severity of follicular hyperkeratosis at trichoscopy.[35]

Table 1: Differential diagnosis of FFA.

Diagnosis	Sex/age (years)	Alopecia pattern	Cicatricial alopecia	Erythema, follicular inflammation	Eyebrow alopecia	Axillary alopecia	Trichoscopic findings	Histopathological features
Frontal fibrosing alopecia	Female Postmeno-pausal	Frontotemporal hair loss: linear, diffuse zig-zag, pseudo fringe	Yes	Yes	Yes	Yes	Follicular hyperkeratosis/ erythema,absence of follicular ostia Yellow dots, Hair diameter variability	Lymphohistiocytic infiltrate around isthmus and infundibular region of hair follicle,
Lichen planopilaris	Female 40	Multiple plaques predominant in vertex and parietal areas	Yes	Yes	No	No	Follicular scale, white dots, reduced follicular ostia	Concentric follicular lamellar fibrosis
Traction alopecia	Young Female	Recession of frontotemporal hairline Irregular borders and broken hair	Yes	No	No	No	Miniaturized hairs, white dots, fracture hair shafts	No lymphocytic inflammation Follicular fibrosis
Androgenetic alopecia	Female Middle aged-elderly	Diffuse Spares the frontal hairline	No	No	No	No	Hair diameter variability, yellow dots	Miniaturization of follicles Superficial perivascular infiltrate
Alopecia areata	Mean age ranging 30 to 40	Unique or multiple plaques Ophiasis	No	No	Yes	No	Dystrophic hair, yellow dots	Peribulbar lymphocytic infiltrate

TREATMENT

As shown, there is no standardized assessment method, not allowing for comparable data. Thus, evidence supporting any treatment for primary cicatricial alopecia is universally scarce with no established guidelines.[16]

The fundamentals of therapy consist in slowing down or stopping hair loss, reducing inflammatory areas and controlling patient symptoms.[36] The choice of treatment may attend to location, symptoms, inflammation and disease stage.[1]

Topical corticosteroids are generally considered first-line agents or mostly used as adjuvants. Some patients lay on them for extensive periods, evidencing the spread of an interfollicular vascular net, despite the absence of follicular erythema and the risk of skin atrophy.[37] Strazzulla et al showed that topical tacrolimus, a calcineurin inhibitor might have a place on the treatment of FFA. A retrospective cohort study comparing topical tacrolimus 0.3% and betamethasone/clobetasol showed a statistically significant result on stabilization of FFA (within first three months) in the group treated with tacrolimus.[38] While oral cyclosporine has demonstrated favourable evidence for LPP treatment, it was only tried in one FFA patient. Adverse effects, such as perioral numbness and tingling, led to therapy suspension.[36]

In targeted alopecia areas, intralesional triamcinolone acetonide (ITA) injections are endorsed.[39] Donovan and Banka et al demonstrated positive results using ITA concentrations of 2.5 mg/mL with 0.5-3 mL and 10 mg/mL with 0.125 mL, respectively.[40,41] Although, the applied methodology was diverse: Donovan et al considered an erratic administration of ITA (variable dosage and intervals), while Banka at al achieved favourable results with fixed injection intervals (6 to 8 weeks) during a total of 4 to 5 sessions.[40,41]

A randomized controlled trial comparing isotretinoin 20 mg/day plus topical treatments and monotherapy with topical agents evidenced a statistically significant response in the combined group. Both hair regression and facial papules have shown amelioration.[42] Rakowska et al even demonstrated the efficacy related to oral retinoids, at the expense of 5α reductase inhibitors. Taking isotretinoin 20 mg/day or acitretin 20 mg/day was more frequently linked with disease stagnation after 12 months of therapy, compared to finasteride 5 mg/day. Interestingly, this retrospective study have also reported no further progression after therapy discontinuation.[43] These outcomes are in agreement with the reported anti-fibrotic properties of oral retinoids, but adverse effects, such as teratogenicity, elevation of liver enzymes and mood depression should be taken into account.[43]

The 5α-reductase inhibitors were also pointed as a possible treatment of FFA, regarding the hormonal hypothesis. Finasteride inhibits selectively type-II 5α-reductase, while dutasteride blocks both type I and type II, leading to a more powerful suppression of DHT. However, its powerful activity may reflect a greater number of adverse effects, compared to finasteride. Teratogenicity, doubtful association with breast cancer, reduced libido and humor disturbances have been reported.[44] A retrospective multicenter study included 355 patients. 111 (31%) of them have taken finasteride 2.5-5.0 mg/day or dutasteride 0.5 mg/week with a mean time follow-up of 2.1 years. 52 (47%) patients showed improvement, as long as 59 (53%) had no further progression of the disease.[12] This study represents the highest quality evidence of using 5α-reductase inhibitors in FFA. Nevertheless, considerations regarding the 144 (41%) patients having androgenetic alopecia should be taken into consideration as possible confounders.[1,12]

Antimalarials, such as hydroxychloroquine and chloroquine diphosphate are frequently used in FFA treatment, due to their established antilymphocyte response. Side effects comprehend gastrointestinal (nausea, vomiting, diarrhoea) and neuromuscular symptoms (headache, myalgia, fatigue), highlighting maculopathy.[45] In 2016, the American Academy of Ophthalmology recommended a baseline fundus examination within the first year of treatment with annual screening after 5 years for patients on adequate doses, without other major risk factors, such as renal impairment.[46]

Samrao et al in a retrospective review of 36 patients evaluated the effects of both doxycycline and mycophenolate mofetil. Although, no assumptions can be made, considering the initial small sample size and subsequent drop outs.[31]

Newer potential therapies embrace PPAR-γ agonists (pioglitazone), opioid antagonists (naltrexone), Janus kinase (JAK) inhibitors (tofacitinib) and hair transplantation. Pioglitazone is used for decades in type 2 diabetes, gaining a new purpose as the role of PPAR-γ in supressing fibrosis has been reaffirmed. Precautions related to weight gain and oedema, predisposing to aggravation of heart failure have to be taken into account.[9] On the other hand, low-dose naltrexone (3 mg/day) maybe beneficial on pruritus, inflammation and FFA evolution with tolerable side effects.[47] The efficacy of tofacitinib has been tested in 2 FFA patients, but it seems to be related to inhibition of interferon inflammation signaling.[48] More recently, Plante et al showed positive clinical response with both topical and oral formulations, regarding small sample size (9 patients) and clinical diagnosis in nearly half of the participants.[49]

Nusbaum and Jiménez et al demonstrated 3 cases with initial regrowth during the first 15 to 24 months after hair transplant. Though, more than half of the transplanted hairs had been lost after 3 years. Longer stabilization of the disease (from 1 to 5 years) as well as maintenance

and adherence of medical therapy after hair transplantation have been indicated as protective factors.[50]

PROGNOSIS

Expectations should be managed as regrowth only occurs in rare cases.[16] FFA is characterized by a gradual evolution with spontaneous stabilization, which can be a possible confound in research studies.[36] Although, less commonly reported, pseudo fringe pattern presents the best prognosis.[18] Contrarily, diffuse zig zag pattern is characterized by the worst prognosis.[18]

CONCLUSION

This study aimed to review the current state of the art related to FFA. Multiple authors have been researching on pathogenesis and management of the disease towards the enrichment of well-being.

A comprehensive analysis supports an early recognition of FFA, enabling an early beginning of therapy, which can lead to a lesser extent of hair loss. However, randomized controlled trials and prospective studies are needed for a standardized treatment through the usage of uniform assessment methods.

Spontaneous stabilization of FFA can occur, but duration until then remains unknown. Expectations should always be managed as regrowth only occurs in rare cases.

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